DRAFT

METHIDATHION

RISK CHARACTERIZATION DOCUMENT

Executive Summary

Department of Pesticide Regulation
California Environmental Protection Agency

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Introduction

The Department of Pesticide Regulation (DPR) conducts risk assessments for pesticides used in California to determine whether the use poses a present or potential human health hazard in California. Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations. This type of assessment includes a quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. After the completion of the risk assessment, the risk management phase takes place at DPR. Risk management refers to the process by which policy actions are chosen to deal with hazards identified in the risk assessment process. Risk managers consider scientific evidence and risk estimates, along with statutory, engineering, economic, social, and political factors, in evaluating alternative regulatory options and choosing among those options.

Risk assessments are mandated by Senate Bill (SB) 950, the Birth Defect Prevention Act, and Assembly Bills (AB) 1807 and 3219. Under SB 950, the risk assessment is comprehensive and considers the potential exposures of various population groups, which may include workers, residents, and bystanders, depending on how the pesticide is used. Bystander is defined as any person not directly involved with the fumigation process, but is in the vicinity of the fumigation site. For each group, multiple routes of exposure, when appropriate, are assessed. These include inhalation via the air, absorption through the skin, and consumption of treated food. In comparison, AB 1807 and 3219 establish a procedure for identification and control of toxic air contaminants (TACs) in California. The statutes define toxic air contaminants as air pollutants that may cause or contribute to an increase in mortality or in serious illness, or that may pose a present or potential hazard to human health. DPR TAC program focuses on the evaluation and control of pesticides in ambient community air.

This report describes the risk assessment for the inhalation exposure to methidathion in the product Supracide® 2E, under both SB 950 and AB 1807 mandates. In preparing this report, DPR staff reviewed pertinent scientific literature and reports through the Fall of 2005. Based on the results of this comprehensive evaluation, the Director of DPR will determine whether methidathion is a TAC, and whether mitigation measures are needed to reduce the exposure by the workers and the general population in California. If methidathion is designated a TAC, the risk management provisions of the law mandate the DPR to determine the need for and develop appropriate control measures for methidathion uses in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), the Air Resources Board, the air pollution districts, air quality management districts, and county agricultural commissioners of the affected counties.

What is contained in the report?

This report evaluates the potential for methidathion exposure and includes:

- A review of the available scientific evidence on methidathion and its oxon regarding their physical properties, sources in the environment, and fates in the environment;
- Summary of toxicology studies conducted with methidathion and its oxon;

- Estimates of human exposure to airborne methidathion and its oxon; and
- An assessment of the risk to humans resulting from current or anticipated exposure to airborne methidathion and its oxon.

What is methidathion, what are the primary sources of methidathion in the environment, and how it is used?

Methidathion is a colorless crystal belonging to the chemical family of organophosphates, and sub-class phosphorodithioates. It is sparingly soluble in water and readily soluble in common organic solvents. It is hydrolyzed in alkaline and strongly acidic media and relatively stable to hydrolysis in neutral and slightly acidic media. The common molecular formula is $C_6H_{11}N_2O_4PS_3$. The molecular weight is 302.33 g/mole. It has low volatility and the vapor pressure is 3.37×10^{-6} mm Hg (25 ^{0}C), and the Henry's Law Constant is 1.95×10^{-9} atm.m-mol.

The source of methidathion in the environment is from its use as a pesticide in agriculture. Methidathion is a non-systemic insecticide/acaricide used to control sucking and chewing insects in a wide variety of crops. It is available in emulsifiable concentrate and soluble powder formulations, which have signal word "Danger/Poison", and another soluble powder formulation with the signal word "Warning". As of June 28, 2005, there were three registered pesticides containing methidathion.

Methidathion is applied by aerial or calibrated power-operated ground equipment. Application rates may vary from 0.25 to 5.0 pounds active ingredient (a.i.) per acre. Methidathion use in California in 2003 was 54,398 pounds, and the peak use of 370, 087 pounds was in 1994. The decline in use started in 1998 and has continued till 2003 where the latest use reports are available. Among the counties, Tulare was the major user in 1994, and Tulare, Kern and Fresno are current leading users. Of the months, December and January see the most pounds applied followed by June and July. Oranges and Almonds continue to be the leading receivers of methidathion.

What is the fate of methidathion in the environment?

Chemical hydrolysis of methidathion in aqueous media shows a rapid decline (shorter half-life) with increase in temperature (41 days at 20 ^{0}C to 0.08 days at 70 ^{0}C, pH1). This becomes accelerated (half-life of 2.8 d. at 20^{0}C to 0.05 d. at 50 ^{0}C, pH 10) with the increase in alkalinity. Photolysis half-life ($T_{1/2}$) was found to be 11 d. at pH 7. Methidathion half-life in soil varied with the characteristics of the soil, and varied from 5 to 30 days. Under dark conditions this may linger much longer (half-life of 124 days). Biodegradation under aerobic conditions is rapid (3.1 d. half-life), and in the absence of air it took little longer. Methidathion has been detected in California river systems in several investigations. Methidathion residues have been found in a variety of food and other products, and when stored under cool, dark conditions may persist for years.

Little is known about the atmospheric fate mechanisms. Atmospheric OH^- radicals are said to be the most reactive with methidathion in air and the estimated lifetimes vary from 0.8 hours to 2 days. However, methidathion has been reported to travel faraway from the application sites.

This pesticide has been detected in air of Sequoia National Park while the applications take place in the citrus orchards in Exeter area of the foothills. It has also been detected in the air in locations closer to filed applications.

Who will be exposed to methidathion, and what are the exposure levels?

Individuals might be exposed to methidathion if they live, work, or perform other activities adjacent to fields that are being treated or have recently been treated (bystander exposure). Also, air monitoring studies in Tulare County suggest that airborne methidathion exposures to the public are possible in areas that are far from application sites (ambient air exposure). In this report, exposures are expressed as absorbed doses, which accounts for differences in the age-related inhalation rate, and in the exposure duration under the various scenarios. For ambient air exposures, durations are acute (i.e., intervals of 7 days or less), seasonal (intermediate-term intervals, lasting from one week to one year), and annual. For bystanders, the exposures are primarily acute durations.

Bystander exposures to airborne methidathion were estimated based on data from air monitoring of methidathion and its reaction product, methidathion oxon, 15 – 150 meters from the edge of an orange grove during an application. The estimated acute exposures of bystanders to methidathion were 0.00177 mg/kg/day for infants and 0.00087 mg/kg/day for adults. The estimated acute exposures of bystanders to methidathion oxon were 0.00052 mg/kg/day for infants and 0.00026 mg/kg/day for adults. These estimates were based on a 24-hour time-weighted average concentration and an assumption of typical activity levels. As available information suggests that exposures of less than 24 hours can result in toxicity, 1-hour absorbed dose estimates were calculated as well, based on the highest measured concentrations and an assumption of heavy activity. These 1-hour absorbed dose estimates for methidathion were 0.00315 mg/kg/hr for infants and 0.00057 mg/kg/hr for adults. The 1-hour absorbed dose estimates for methidathion oxon were 0.00019 mg/kg/hr for infants and 0.000034 mg/kg/hr for adults. Seasonal and annual exposures for bystanders were not estimated, because airborne concentrations are anticipated to reach ambient levels within a few days after each application and limited numbers of applications are allowed by product labels.

Ambient air exposures were estimated based on monitoring of methidathion and its reaction product, methidathion oxon, in ambient air. The range of estimated acute exposures to methidathion in ambient air were 0.000110 mg/kg/day for infants and 0.000052 mg/kg/day for adults. The range of estimated acute exposures to methidathion oxon in ambient air were 0.000047 mg/kg/day for infants and 0.000022 mg/kg/day for adults. Seasonal exposures to methidathion were estimated to be 0.000041 mg/kg/day for infants and 0.000019 mg/kg/day for adults. Seasonal exposures to methidathion oxon were estimated to be 0.000019 mg/kg/day for infants and 0.000009 mg/kg/day for adults. Annual exposures to methidathion were estimated to be 0.000031 mg/kg/day for infants and 0.000014 mg/kg/day for adults. Annual exposures to methidathion oxon were estimated to be 0.000014 mg/kg/day for infants and 0.000007 mg/kg/day for adults.

What are the potential health effects from acute and repeated exposures to methidathion?

Acute or short-term exposure to methidathion resulted in neurological signs that were due to its inhibition of the enzyme, acetylcholinesterase (AChE), in the central and peripheral nervous systems that is involved in the termination of nerve impulses between certain types of nerves. The cholinergic signs observed in laboratory animals after acute exposure to methidathion included lack of muscle coordination, twitching, convulsions, excessive salivation and tearing, and difficulty in breathing. The No-Observed-Effect Level (NOEL) in an acute oral neurotoxicity study was estimated to be 0.3 mg/kg based on a significant reduction of AChE activity in the cerebral cortex of male rats.

Brain AChE inhibition and cholinergic signs similar to those observed with acute exposure were also observed in laboratory animals after subchronic exposure. In addition, reduced body temperatures, reduced body weights and food consumption, hematological changes suggestive of anemia, changes in serum enzyme levels suggestive of liver toxicity, and lesions in the liver, gallbladder, stomach, kidney and heart were seen. The lowest subchronic NOEL was 0.2 mg/kg/day that was observed in a 90-day neurotoxicity study in rats based reduced AChE activity in RBCs and various brain regions in both sexes. AChE inhibition in RBCs was considered a surrogate for AChE inhibition in the peripheral nervous system which was not measured in this study.

Several developmental and reproductive effects were seen in studies including reduced pup weights, signs of maternal neglect, and reduced maternal index. The NOELs for fetal or pup effects were equal to or higher than the maternal or parental NOELs, suggesting there is no increased pre- or post-natal sensitivity to methidathion. However, in one direct-dosing study where the LD_{50} was determined in both weanling and adult rats, the weanling rats appear to be slightly more sensitive.

The effects observed in laboratory animals with chronic exposure to methidathion were similar to those observed with subchronic exposure, except that evidence of hepatotoxicity was more common. Although both the neurotoxicity and hepatoxicity were seen in most species, the neurotoxicity was more prevalent in rats while dogs appeared to be more sensitive to the hepatotoxicity. The lowest NOEL in a chronic study of acceptable quality was 0.15 mg/kg/day based on elevated liver enzymes in the serum and microscopic lesions in the liver of dogs exposed to methidathion in the diet for 1 year.

Is there any potential cancer risk from exposure to methidathion?

An increase in liver tumors was observed in male mice in two different carcinogenicity studies. The tumors were only observed at dose levels that produced significant increases in other non-neoplastic lesions in the livers of mice suggesting that they maybe secondary to these other liver lesions. However, direct DNA interaction could not be eliminated based on a few positive genetic toxicity tests. Furthermore, no mechanistic data was submitted to support a threshold mechanism. Therefore, it was assumed that a non-threshold mechanism was involved as a default and the cancer potency was estimated to range from 0.34 $(mg/kg/day)^{-1}$ for the maximum likelihood estimate to 0.53 $(mg/kg/day)^{-1}$ for the 95% upper bound estimate.

Does the concentration of methidathion in the air pose a potential health hazard for humans?

The risk for non-carcinogenic health effects can be expressed as a margin of exposure (MOE) which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human population and the sensitive subgroup. The negligible carcinogenic risk level is generally considered 1 excess cancer case in a million.

The MOEs for acute exposure to methidathion in application site air were greater than 100 for both children and adults. The MOEs for acute, seasonal and chronic exposure to methidathion in ambient air were greater than 1,000 for both children and adults. These MOEs are sufficiently high to not require mitigation, but the acute MOEs at the application site are low enough to meet the criteria for identifying methidathion as a toxic air contaminant. The carcinogenic risk estimates for the general public based on the ambient air exposure ranged from 7.1×10^{-6} to 1.1×10^{-5} which is above the negligible risk level of 10^{-6}. This carcinogenic risk level also meets the criteria for identifying methidathion as a toxic air contaminant since the exposure levels are not 10-fold below the negligible carcinogenic risk level. Since this carcinogenic risk level for ambient air is above the negligible risk level mitigation may be needed.

Does methidathion oxon, a degradation product of methidathion, pose a potential health hazard?

Methidathion oxon is a degradation product of methidathion. It is also considered the active metabolite of methidathion with respect to its neurotoxicity and, therefore, presumably as toxic or more toxic than the parent compound. However, no toxicity data was available for methidathion oxon. Methidathion oxon was measured in the air monitoring that was conducted for both application site and ambient air. Exposure to the oxon was added to the parent compound and was assumed to be equally toxic when evaluating risks for both non-cancer and cancer endpoints.